Practitioner's Docket No. U 014929-4 *PATENT*

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: MANNE SATYANARAYANA **REDDY**, et al
Application No.: 10/729,837 Group No.: 1624
Filed: DECEMBER 4, 2003 Examiner: - -
For: POLYMORPHIC FORMS OF ZIPRASIDONE AND ITS HYDROCHLORIDE SALT AND PROCESS FOR PREPARATION THEREOF

Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL OF CERTIFIED COPY

Attached please find the certified copy of the foreign application from which priority is claimed for this case:

Country:	INDIA
Application Number:	907/MAS/2002
Filing Date:	DECEMBER 4, 2002

WARNING: "When a document that is required by statute to be certified must be filed, a copy, including a photocopy or facsimile transmission of the certification is not acceptable." 37 C.F.R. 1.4(f) (emphasis added).

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Signature

Date: APRIL 13, 2004

JANET I. CORD
(type or print name of person certifying)

SIGNATURE OF PRACTITIONER

Reg. No. 33,778

JANET I. CORD
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NOTE: "The claim to priority need be in no special form and may be made by the attorney or agent, if the foreign application is referred to in the oath or declaration, as required by § 1.63." 37 C.F.R. 1.55(a).

U014929-4
Group No.: 1624
S. N. 10/729,837

THE PATENTS ACT, 1970

It is hereby certified that annexed hereto is a true copy of Application, Provisional Specification, Complete Specification, Abstract & Drawings of the extract of Patent Application No.907/MAS/2002, dated 04.12.2002 by Dr. Reddy's Laboratories Limited having its registered office at 7-1-27, Ameerpet, Hyderabad 500 016, Andhra Pradesh, India.

.....

.....**In witness thereof**

I have hereunto set my hand

Dated this the 19h day of February 2004

M. S. V

(M.S. VENKATARAMAN)
ASSISTANT CONTROLLER OF PATENTS & DESIGNS

PATENT OFFICE BRANCH
GOVERNMENT OF INDIA
Guna Complex, 6th Floor, Annex.II
No.443, Anna Salai, Teynampet,Chennai – 600 018

FORM 1

THE PATENTS ACT, 1970
(39 of 1970)
APPLICATION FOR GRANT OF A PATENT
(Section 5(2), 7, 54 and 135 and Rule 33A)

1. I/We, Dr. Reddy's Laboratories Limited, an Indian company having its registered office at 7-1-27, Ameerpet, Hyderabad, Andhra Pradesh, INDIA, 500 016
2. hereby declare -
   (a) that I am/ we are in possession of an invention titled "**Novel polymorphic forms of Ziprasidone hydrochloride and process for preparation thereof**"
   (b) that the Complete specification relating to this invention is filed with this application.
   (c) that there is no lawful ground of objection to the grant of a patent to me/us.
3. further declare that the inventor(s) for the said invention is/are **Manne Satyanarayana Reddy, Srinivasan Thirumalai Rajan, Uppala Venka Bhaskara Rao, Mummadi Venkatesh and Akundi Surya Prabhakar.** All citizens & residents of India belonging to **Dr. Reddy's Laboratories Limited, 7-1-27, Ameerpet, Hyderabad – 500 016, Andhra Pradesh.**
4. I/We claim the priority from the application(s) filed in convention countries, particulars of which are as follows.
5. I/We state that the said invention is an improvement in or modification of the invention, the particulars of which are as follows and of which I/We are the applicant/patantee
6. I/We state that the application is divided out of my/our application, the particulars of which are given below and pray that this application deemed to have been filed on _____ under section 16 of the Act.
7. That I am/We are the assignee or legal representative of the true and first inventors.
8. That my/our address for service in India is as follows:

907/MAS/2002
4-12-2002

24 DEC 2003

ORIGINAL

Sundaram Venkatraman
Vice-President-R&D
Dr. Reddy's Laboratories Limited
7-1-27, Ameerpet
Hyderabad, A.P., 500 016
Phone: 040- 3095578
Fax: 040-3095438

9. Following declaration was given by the inventor(s) or applicant(s) in the convention country:
I/We, the true and first inventors for this invention or the applicant(s) in the convention country declare that the applicant(s) herein is/are my/our assignee or legal representative

(Signed)_____
Manne Satyanarayana Reddy,
H.No. 8-3-167/D/16,
Kalyan Nagar,
Near AG Colony,
Erragadda,
Hyderabad-500 038.

Signed)_____
Srinivasan Thirumalai Rajan,
Plot No. 12,
Lake view Enclave,
Miyapur,
Hyderabad-500 050.

Signed)_____
Uppala Venkata Bhaskara Rao,
MIG-53, Dharma Reddy Colony,
Phase-I, KPHB,
Kukatpally,
Hyderabad – 500 072.

Signed)_____
Mummadi Venkatesh,
H.No.2-32,
Parvathapur,
Uppal,
Hyderabad – 500 039

(Signed)_____
Akundi Surya Prabhakar,
Flat No. 105, Plot No. 35,
Rama Krishna Towers,
Bhagyanagar Colony,
Kukatpally,
Hyderabad – 500 072.

10. That to the best of my/our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to me/us on this application.

11. Following are the attachments with the application
    (a) Complete specification (-13- pages, in triplicate)
    (b) Drawings (-03- pages, in triplicate)
    (c) Priority documents(s)
    (d) Statement and Undertaking on Form-3.
    (e) Power of authority
    (f) Abstract of the invention (-01- page, in triplicate)
    (g) Fee Rs. 5000.00 (five thousand rupees only) in Cash/cheque/bank draft bearing No.336227 dated 27.11.02 drawn on HDFC Bank Limited, Lakdi-ka-pool, Hyderabad – 4.

I/We request that a patent may be granted to me/us for the said invention.

Dated this28th day of November 2002.

(Signed) S. Venkatraman

Sundaram Venkatraman
Vice-President (R&D)
Dr. Reddy's Laboratories Limited.

To,
The Controller of Patents
The Patents Office Branch, Chennai.

FORM 2

THE PATENTS ACT, 1970

PROVISIONAL SPECIFICATION

(SECTION 10)

Novel Polymorphic forms of Ziprasidone hydrochloride and Process for preparation thereof

Dr. Reddy's Laboratories Ltd.

an Indian Company having its registered office at

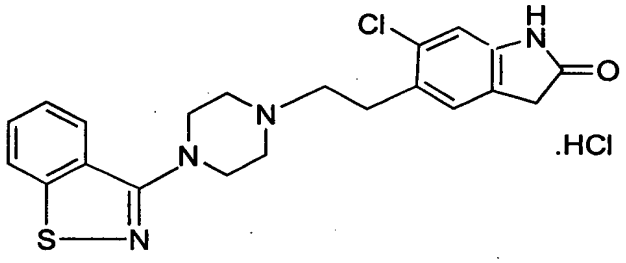
7-1-27, Ameerpet

Hyderabad – 500 016, A.P., India

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

Field of the Invention:

The present invention relates to novel polymorphic forms of Ziprasidone and its hydrochloride, which is chemically known as 5-(2-(4-(1,2-benzisothiozole-3yl)-piperazinyl) ethyl) - 6- chloro-1, 3-dihydro-2H-indole-2-one hydrochloride and shown as Formula (I). The present invention more specifically relates to novel amorphous form of Ziprasidone hydrochloride, novel crystalline forms of Ziprasidone and its hydrochloride. The present invention further relates to the process for the preparation of these novel polymorphic forms of Ziprasidone and its hydrochloride.



Formula (I)

Ziprasidone is useful as Anti psychotic agent used for the treatment of psychotic disorders of the schizophrenic types, and in particular the compounds are useful for removing or ameliorating such symptoms as anxiety, agitation, excessive aggression, tension and social or emotional withdrawal in psychotic patients.

Background of the invention:

US Patent 4,831,031 claims Ziprasidone and its related including the pharmaceutically acceptable salts. USP '031 also discloses the process for the preparation of Ziprasidone hydrochloride and other relative compounds of Ziprasidone.

US Patent 5,312,925 claims Ziprasidone hydrochloride monohydrate along with pharmaceutical composition and method of treating neuroleptic diseases. The said patent

also discloses the hemihydrate and anhydrous forms of Ziprasidone hydrochloride. The hydrate forms and anhydrous forms of Ziprasidone hydrochloride are characterized by their X-ray diffractograms and Infrared spectra. The process for the preparation of Ziprasidone hydrochloride monohydrate comprises treating Ziprasidone base with aqueous hydrochloric acid at 60-65^{O}C and on controlled drying afforded the desired compound.

No other relevant references of Ziprasidone or its pharmaceutically acceptable salts in hydrate or anhydrous form were disclosed the Polymorphic forms till date.

Polymorphism can be defined as the ability of the same chemical substance to exist in different crystalline structures. The different structures are referred to as polymorphs, polymorphic modification or form.

Hence, the first object of the present invention is to provide the novel crystalline form of Ziprasidone and its hydrochloride. The novel crystalline form of Ziprasidone hydrochloride having moisture content in the range of 3.5-4.5%, which indicates the monohydrate.

The second object of the present invention is to provide the novel amorphous form of Ziprasidone hydrochloride having moisture content in the range of 0.5 to 7.5%.

The further object of the present invention is to prepare the novel polymorphic forms of Ziprasidone and its hydrochloride.

The crystalline and amorphous forms of the present invention are characterized by X-ray diffractogram pattern. The XRD pattern obtained for the present inventive substance is well distinguished to the XRD pattern disclosed in USP '925 for Ziprasidone hydrochloride monohydrate.

Hence, the inventors of the present invention are designated the crystalline form disclosed in USP'925 as Form-I and the crystalline form obtained in the present invention as Form-II for Ziprasidone hydrochloride monohydrate, hereinafter the present novel crystalline form is referred as crystalline Form-II of Ziprasidone hydrochloride monohydrate.

The novel crystalline Form-II and amorphous form of Ziprasidone hydrochloride of the present invention may be well suited for pharmaceutical formulations and can be used as anti psychotic agents.

Brief description of accompanying drawings:

Fig-1: X-Ray powder diffractogram of novel crystalline Form-II of Ziprasidone hydrochloride obtained in the present invention.

Fig -2: X-Ray powder diffractogram of novel amorphous form of Ziprasidone hydrochloride obtained in the present invention.

Fig -3: X-Ray powder diffractogram of novel crystalline form of Ziprasidone obtained in the present invention.

Summary of the invention:

The present invention provides novel crystalline forms of Ziprasidone and its hydrochloride, novel amorphous form of Ziprasidone hydrochloride and process for preparation thereof. The novel crystalline form of Ziprasidone hydrochloride of present invention is designated as crystalline Form-II of Ziprasidone hydrochloride monohydrate. The novel polymorphic forms of Ziprasidone and its hydrochloride are characterized by X-ray diffractogram pattern. The process for the preparation of crystalline Form-II comprises the addition of aqueous hydrochloric acid to the reaction mixture of

Ziprasidone in ketone solvents and further heating to reflux temperature, filtering the desired crystalline compound at ambient temperature.

The process for the preparation of novel amorphous form comprises the addition of aqueous hydrochloric acid to the reaction mixture of Ziprasidone in acetic acid as a solvent at 40-50^{o}C, adding water and an alcoholic solvent then further heating to reflux temperature, distillating the solvents completely under reduced pressure to afford the desired amorphous form.

The process for the preparation of novel crystalline form of Ziprasidone comprises the condensation of 6-Chloro-5-(2-Chloroethyl) Oxindole with 3-(1-piperazinyl)-1,2-benzisothiozole in water using sodium carbonate and it is purified in acetone to afford the crude Ziprasidone. The crude Ziprasidone is treated with methane sulfonic acid in methanol media to afford the mesylate salt, thus resulted salt is desaltified with caustic lye in water media to afford the novel crystalline form.

Detailed description of the invention:

The present invention provides the novel crystalline Form-II, amorphous form of Ziprasidone hydrochloride, novel crystalline form of Ziprasidone and process for preparation there of.

The crystalline Form-II of Ziprasidone hydrochloride obtained in the present invention is having moisture content in the range 3.5 to 4.5% by KF, which indicates the monohydrate.

The amorphous form of Ziprasidone hydrochloride obtained in the present invention is having moisture content in the range of 0.5 to 7.5% by KF.

The moisture content of present inventive substances was measured on Mettler DL-35 instrument using Karl-Fischer reagent.

The polymorphic forms of Ziprasidone and its hydrochloride of present invention is characterized by X-ray diffractogram, which are measured on Bruker Axe, DS Advance Powder X-ray Diffractometer with Cu K alpha-1 Radiation source.

The characteristic X-ray diffractograms of crystalline Form-II, amorphous form of Ziprasidone hydrochloride and crystalline form of Ziprasidone of present invention are substantially as depicted in Figure (1), (2) and (3) respectively.

The process for the preparation of novel crystalline Form-II of Ziprasidone hydrochloride comprises:

(i) suspending the Ziprasidone base in ketone solvents, preferably acetone;

(ii) adding aqueous hydrochloric acid solution;

(iii) heating the reaction mixture to reflux temperature and further stirring for 1-2 hours;

(iv) cooling the reaction mixture to ambient temperature;

(v) filtering the solid by conventional methods and further drying at 50-100^{O}C to a constant weight to afford the title crystalline solid.

The crystalline Form-II of Ziprasidone hydrochloride obtained in the above process is characterized by the X-ray powder diffraction pattern. The characteristic 2-theta values (in degrees) of the identified peaks in the X-ray diffractogram are 9.870, 15.321, 24.627, 26.526, 22.898, 25.249, 25.502, 18.092, 13.308 and 28.488.

The process for the preparation of novel amorphous form of Ziprasidone hydrochloride comprises:

a) suspending the Ziprasidone base in acetic acid;

b) adding aqueous hydrochloric acid solution at 40-50^{O}C;

c) adding water and an alcoholic solvent, preferably isopropyl alcohol;

d) further heating to reflux temperature and stirring for 1-2 hours;

e) distilling the solvents completely under reduced pressure till the solid separates out;

f) taking out the solid and further drying at 50-100^{O}C to afford the title amorphous form.

The amorphous form of Ziprasidone hydrochloride obtained in the above process is characterized by the X-ray powder diffraction pattern, which is having no well-resolved peaks.

The process for the preparation of novel crystalline form of Ziprasidone comprises the condensation of 6-Chloro-5-(2-Chloroethyl) Oxindole with 3-(1-piperazinyl)-1,2-benzisothiozole in water using sodium carbonate and it is purified in acetone to afford the crude Ziprasidone. The crude Ziprasidone is treated with methane sulfonic acid in methanol media to afford the mesylate salt, thus resulted salt is desaltified with caustic lye in water media to afford the novel crystalline form.

The crystalline of Ziprasidone obtained in the above process is characterized by the X-ray powder diffraction pattern. The characteristic 2-theta values (in degrees) of the identified peaks in the X-ray diffractogram are 16.335, 12.209, 25.156, 27.019, 24.21, 5.255 and 18.511.

The novel crystalline Form-II and amorphous forms of Ziprasidone hydrochloride of present invention are well suited for pharmaceutical applications.

The processes of the present invention are simple, non-hazardous and easily scalable.

Dated: 29th day of November 2002.

Signed)_____

Dr. Manne Satyanarayana Reddy,
Vice-President (R&D),
Dr. Reddy's Laboratories Limited.

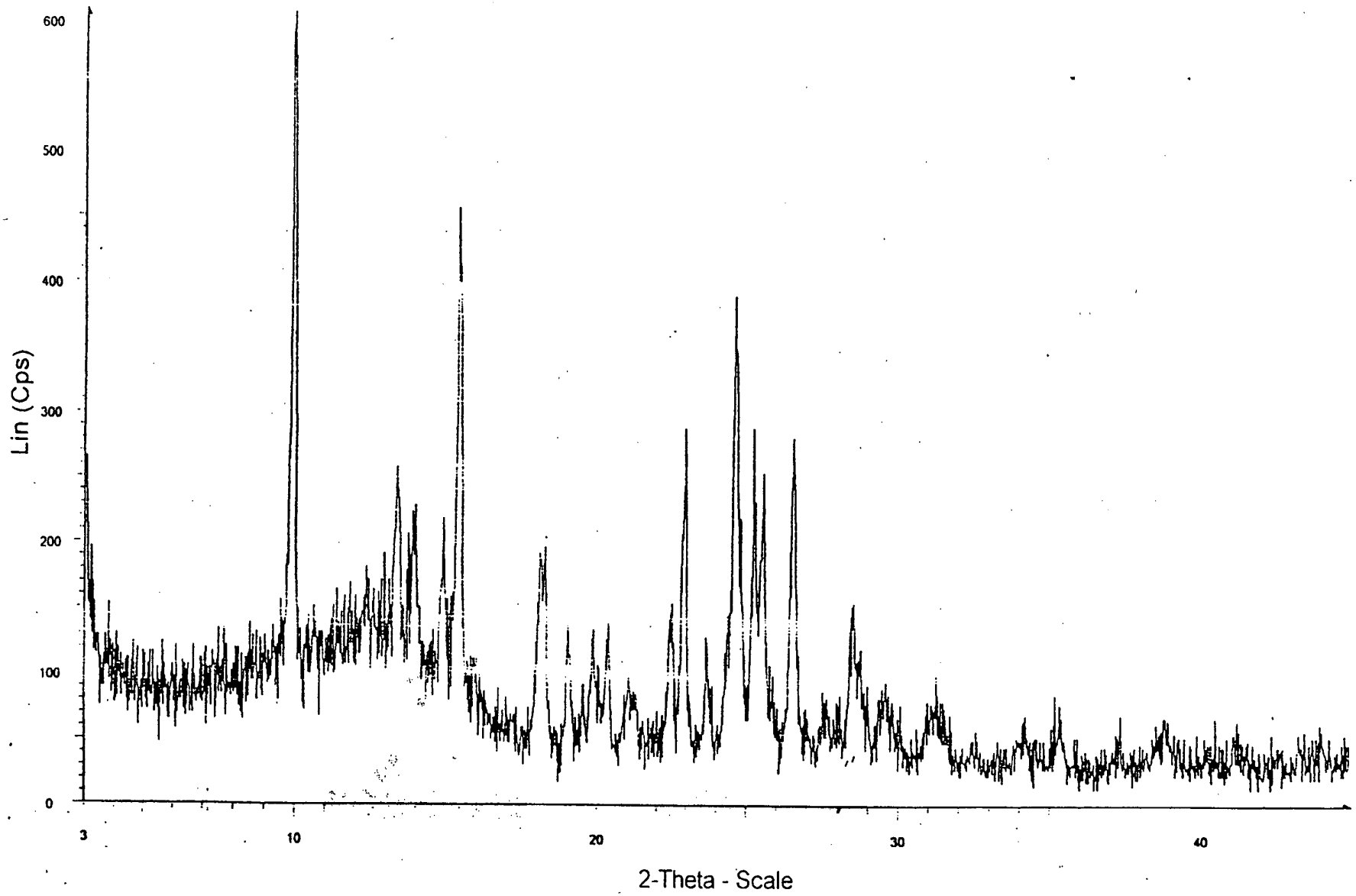


Fig. 1

MANNE SATYANARAYANA REDI

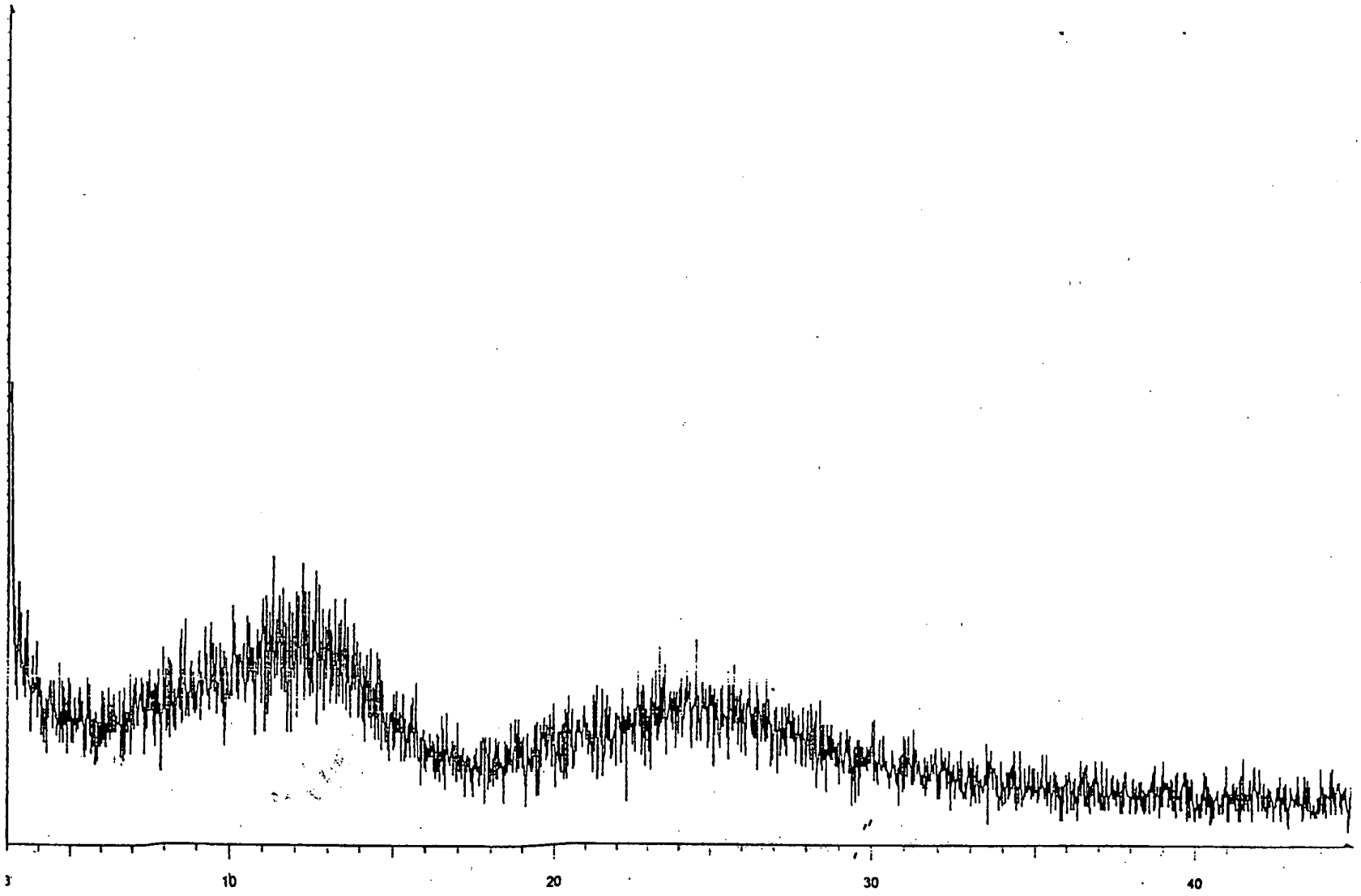
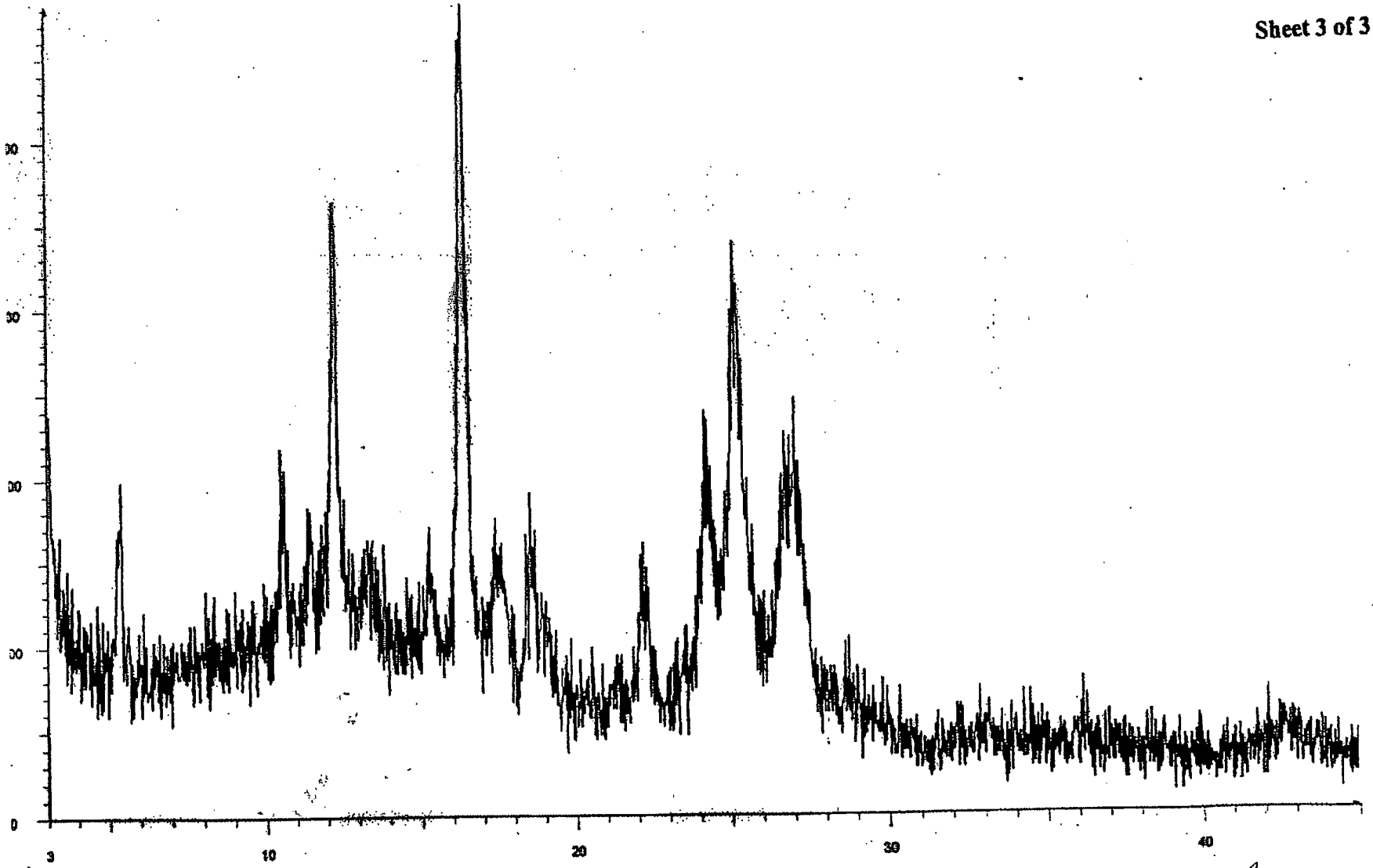


Fig. 2

MANNE SATYANARAYANA REDDY



MANNE SATYANARAYANA REDDY

Fig. 3

FORM 2

THE PATENTS ACT, 1970

COMPLETE SPECIFICATION

(SECTION 10)

907/MAS/2002
4-12-2002

Novel Polymorphic forms of Ziprasidone hydrochloride and Process for preparation thereof

04 DEC 2003

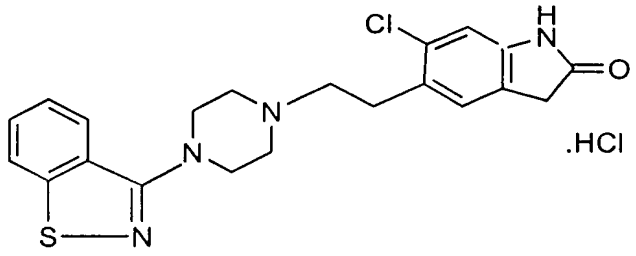
ORIGINAL

Dr. Reddy's Laboratories Ltd.
an Indian Company having its registered office at
7-1-27, Ameerpet
Hyderabad – 500 016, A.P., India

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

Field of the Invention:

The present invention relates to novel polymorphic forms of Ziprasidone and its hydrochloride, which is chemically known as 5-(2-(4-(1,2-benzisothiozole-3yl)-piperazinyl) ethyl) - 6- chloro-1, 3-dihydro-2H-indole-2-one hydrochloride and shown as Formula (I). The present invention more specifically relates to novel amorphous form of Ziprasidone hydrochloride, novel crystalline forms of Ziprasidone and its hydrochloride. The present invention further relates to the process for the preparation of these novel polymorphic forms of Ziprasidone and its hydrochloride.



Formula (I)

Ziprasidone is useful as Anti psychotic agent used for the treatment of psychotic disorders of the schizophrenic types, and in particular the compounds are useful for removing or ameliorating such symptoms as anxiety, agitation, excessive aggression, tension and social or emotional withdrawal in psychotic patients.

Background of the invention:

US Patent 4,831,031 claims Ziprasidone and its related including the pharmaceutically acceptable salts. USP '031 also discloses the process for the preparation of Ziprasidone hydrochloride and other relative compounds of Ziprasidone.

US Patent 5,312,925 claims Ziprasidone hydrochloride monohydrate along with pharmaceutical composition and method of treating neuroleptic diseases. The said patent

also discloses the hemihydrate and anhydrous forms of Ziprasidone hydrochloride. The hydrate forms and anhydrous forms of Ziprasidone hydrochloride are characterized by their X-ray diffractograms and Infrared spectra. The process for the preparation of Ziprasidone hydrochloride monohydrate comprises treating Ziprasidone base with aqueous hydrochloric acid at 60-65^{o}C and on controlled drying afforded the desired compound.

No other relevant references of Ziprasidone or its pharmaceutically acceptable salts in hydrate or anhydrous form were disclosed the Polymorphic forms till date.

Polymorphism can be defined as the ability of the same chemical substance to exist in different crystalline structures. The different structures are referred to as polymorphs, polymorphic modification or form.

Hence, the object of the present invention is to provide a novel amorphous form of Ziprasidone hydrochloride.

The object of the present invention is to provide a novel crystalline form of Ziprasidone and its hydrochloride.

The further object of the present invention is to prepare the novel polymorphic forms of Ziprasidone and its hydrochloride.

The crystalline and amorphous forms of the present invention are characterized by X-ray diffractogram pattern. The XRD pattern obtained for the present inventive substance is well distinguished to the XRD pattern disclosed in USP '925 for Ziprasidone hydrochloride monohydrate.

Hence, the inventors of the present invention are designated the crystalline form disclosed in USP'925 as Form-I and the crystalline form obtained in the present invention

as Form-II for Ziprasidone hydrochloride monohydrate, hereinafter the present novel crystalline form is referred as crystalline Form-II of Ziprasidone hydrochloride monohydrate.

The novel crystalline Form-II and amorphous form of Ziprasidone hydrochloride of the present invention may be well suited for pharmaceutical formulations and can be used as anti psychotic agents.

Summary of the invention:

The present invention provides novel amorphous form of Ziprasidone hydrochloride, novel crystalline forms of Ziprasidone and its hydrochloride and process for preparation thereof. The novel crystalline form of Ziprasidone hydrochloride of present invention is designated as crystalline Form-II of Ziprasidone hydrochloride monohydrate.

The process for the preparation of novel amorphous form comprises the addition of aqueous hydrochloric acid to the reaction mixture of Ziprasidone in acetic acid as a solvent at 40-50^{O}C, adding water and an alcoholic solvent then further heating to reflux temperature, distilling the solvents completely under reduced pressure to afford the desired amorphous form.

The process for the preparation of crystalline Form-II comprises the addition of aqueous hydrochloric acid to the reaction mixture of Ziprasidone in ketone solvents and further heating to reflux temperature, filtering the desired crystalline compound at ambient temperature.

The process for the preparation of novel crystalline form of Ziprasidone comprises the condensation of 6-Chloro-5-(2-Chloroethyl) Oxindole with 3-(1-piperazinyl)-1,2-benzisothiozole in water using sodium carbonate and it is purified in acetone to afford the

crude Ziprasidone. The crude Ziprasidone is treated with methane sulfonic acid in methanol media to afford the mesylate salt, thus resulted salt is desaltified with caustic lye in water media to afford the novel crystalline form.

Brief description of accompanying drawings:

Fig-1: X-Ray powder diffractogram of novel amorphous form of Ziprasidone hydrochloride obtained in the present invention.

Fig -2: X-Ray powder diffractogram of novel crystalline Form-II of Ziprasidone hydrochloride obtained in the present invention.

Fig -3: X-Ray powder diffractogram of novel crystalline form of Ziprasidone obtained in the present invention.

Detailed description of the invention:

The present invention provides the novel amorphous form, crystalline Form-II of Ziprasidone hydrochloride, novel crystalline form of Ziprasidone.

The present invention also provides process for preparation of the novel amorphous form, crystalline Form-II of Ziprasidone hydrochloride, novel crystalline form of Ziprasidone.

The novel polymorphic forms of Ziprasidone and its hydrochloride are characterized by X-ray diffractogram pattern. The X-ray diffraction pattern is measured on Bruker Axe, DS Advance Powder X-ray Diffractometer with Cu K alpha-1 Radiation source.

The characteristic X-ray diffractograms of amorphous form ,crystalline Form-II of Ziprasidone hydrochloride and crystalline form of Ziprasidone of present invention are substantially as depicted in Figure (1), (2) and (3) respectively.

The process for the preparation of novel amorphous form of Ziprasidone hydrochloride comprises:

a) suspending the Ziprasidone base in acetic acid;

b) adding aqueous hydrochloric acid solution at 40-50^{O}C;

c) adding water and an alcoholic solvent comprising of methanol, ethanol, n-propanol, isopropanol, n-butanol, secondary butanol or tertiary butanol, preferably isopropyl alcohol;

d) further heating to reflux temperature and stirring for 1-2 hours;

e) distilling the solvents completely under reduced pressure till the solid separates out;

f) taking out the solid and further drying at 50-100^{O}C to afford the title amorphous form.

The amorphous form of Ziprasidone hydrochloride obtained in the above process is characterized by the X-ray powder diffraction pattern, which is having no well-resolved peaks. The amorphous form of Ziprasidone hydrochloride obtained in the present invention is having moisture content in the range of 0.5 to 7.5% by KF.

The moisture content of present inventive substances was measured on Mettler DL-35 instrument using Karl-Fischer reagent.

The process for the preparation of novel crystalline Form-II of Ziprasidone hydrochloride comprises:

(i) suspending the Ziprasidone base in ketone solvents, preferably acetone;

(ii) adding aqueous hydrochloric acid solution;

(iii) heating the reaction mixture to reflux temperature and further stirring for 1-2 hours;

(iv) cooling the reaction mixture to ambient temperature;

(v) filtering the solid by conventional methods and further drying at 50-100^{O}C to a constant weight to afford the title crystalline solid.

The crystalline Form-II of Ziprasidone hydrochloride obtained in the above process is characterized by the X-ray powder diffraction pattern. The characteristic 2-theta values (in degrees) of the identified peaks in the X-ray diffractogram are 9.870, 15.321, 24.627, 26.526, 22.898, 25.249, 25.502, 18.092, 13.308 and 28.488.

The crystalline Form-II of Ziprasidone hydrochloride obtained in the present invention is having moisture content in the range 3.5 to 4.5% by KF; hence the inventive substance is referred as monohydrate.

The process for the preparation of novel crystalline form of Ziprasidone comprises the condensation of 6-Chloro-5-(2-Chloroethyl) Oxindole with 3-(1-piperazinyl)-1,2-benzisothiozole in water using sodium carbonate and it is purified in acetone to afford the crude Ziprasidone. The crude Ziprasidone is treated with methane sulfonic acid in methanol media to afford the mesylate salt, thus resulted salt is desaltified with caustic lye in water media to afford the novel crystalline form.

The crystalline of Ziprasidone obtained in the above process is characterized by the X-ray powder diffraction pattern. The characteristic 2-theta values (in degrees) of the identified peaks in the X-ray diffractogram are 16.335, 12.209, 25.156, 27.019, 24.21, 5.255 and 18.511.

The crystalline form of Ziprasidone hydrochloride monohydrate II of the present invention is stable at ambient conditions as the hydrate nature of this crystalline form is as such remained.

The novel crystalline Form-II and amorphous forms of Ziprasidone hydrochloride of present invention are well suited for pharmaceutical applications.

The processes of the present invention are simple, non-hazardous and easily scalable.

Example:

The following examples illustrate the invention but do not limit the scope of further invention.

Example 1

Preparation of amorphous form of Ziprasidone hydrochloride

Taken 5 gms of Ziprasidone base and 50 ml of acetic acid into round bottom flask and heated to 45 – 50°C. Added 25 ml of aqueous hydrochloric acid slowly to the mixture over 20 min. Then heating was given for reflux. Added 10 ml of water followed by 50 ml of Isopropanol. Cooled the reaction mass to 50°C and distilled off solvent completely under vacuum. The material formed was scratched from the flask.

Example 2

Preparation of crystalline form of Ziprasidone hydrochloride monohydrate-II

Taken 5 gms of Ziprasidone base and 100 ml of acetone into round bottom flask. Added 25 ml of aqueous hydrochloric acid over 5 min at 32°C. Refluxed the reaction mass for 1 hr 45 min and then cooled to 30-35°C. Filtered the compound and washed with 10 ml of acetone. Dried the compound at 100°C to get 4.5 gms of the Ziprasidone hydrochloride monohydrate crystalline form.

Example 3

Preparation of crystalline form of Ziprasidone

Taken 56.3 gms of sodium carbonate and 500 ml of water into round bottom flask. Added 50 gms of 3-(1-piperazinyl)-1,2-benzisothiazole hydrochloride and 50 gms of 6-Chloro-5-(2-Chloroethyl) oxindole. Refluxed the reaction mixture for 15 hrs. reaction completion is monitored by TLC. Cooled the reaction mass to room temperature and filtered and washed with 50 ml of water. Taken the wet compound and 250 ml of acetone into flask and stirred at room temperature for 2 hrs. Filtered the compound and washed with 50 ml of acetone. Taken wet compound and 750 ml of methanol into the flask and heated to 50°C and added 14 ml of methane sulfonic acid over 20 min. Cooled the reaction mass to room temperature and filtered the compound and washed with methanol. Taken wet compound and 750 ml of water into flask then pH was adjusted to 9 with caustic lye. Stirred at room temperature for 1 hr and filtered the compound. The compound was washed with water and dried at 70°C to get 65 gms of crystalline form Ziprasidone base.

DETAILED DESCRIPTION OF THE ACCOMPANYING DRAWINGS

Fig. 1 is a characteristic X-ray powder diffraction pattern of novel amorphous form of Ziprasidone hydrochloride obtained in the present invention.

Fig. 2 is a characteristic X-ray powder diffraction pattern of novel crystalline form of Ziprasidone hydrochloride monohydrate-II obtained in the present invention.

Vertical axis: Intensity (CPS); Horizontal axis: Two Theta (degrees).

The significant values are 9.870, 15.321, 24.627, 26.526, 22.898, 25.249, 25.502, 18.092, 13.308 and 28.488 two-theta degrees.

Fig. 3 is a characteristic X-ray powder diffraction pattern of novel crystalline form of Ziprasidone obtained in the present invention.

Vertical axis: Intensity (CPS); Horizontal axis: Two Theta (degrees).

The significant values are 16.335, 12.209, 25.156, 27.019, 24.21, 5.255 and 18.511 two-theta degrees.

We claim,

1. A Novel amorphous Form of Ziprasidone hydrochloride.
2. The amorphous Form of Ziprasidone hydrochloride of claim 1 having X-ray powder diffraction pattern substantially as depicted in Figure (1).
3. The process for the preparation of novel amorphous form of Ziprasidone hydrochloride comprises:
   a) suspending the Ziprasidone base in acetic acid;
   b) adding aqueous hydrochloric acid solution at 40-50^{O}C;
   c) adding water and an alcoholic solvent comprising of methanol, ethanol, n-propanol, isopropanol, n-butanol, secondary butanol or tertiary butanol, preferably isopropyl alcohol;
   d) further heating to reflux temperature and stirring for 1-2 hours;
   e) distilling the solvents completely under reduced pressure till the solid separates out;
   f) taking out the solid and further drying at 50-100^{O}C to afford the title amorphous form.
4. The process according to claim 3 step (c), wherein alcoholic solvent is isopropyl alcohol.
5. A Novel crystalline Form of Ziprasidone hydrochloride monohydrate II.
6. The crystalline Form of Ziprasidone hydrochloride monohydrate II according to claim 5 characterized by the X-ray powder diffraction pattern: (d values in A^{o}): 9.870, 15.321, 24.627, 26.526, 22.898, 25.249, 25.502, 18.092, 13.308 and 28.488 two-theta degrees.

7. The crystalline Form of Ziprasidone hydrochloride monohydrate II of claim 5 and 6 having X- ray powder diffraction pattern substantially as depicted in Figure (1).

8. The crystalline Form of Ziprasidone hydrochloride monohydrate II according to Claim 5 having the moisture content in a range of 3.0 to 4.5% by KF method.

9. The process for the preparation of novel crystalline Form-II of Ziprasidone hydrochloride comprises:

(i) suspending the Ziprasidone base in ketone solvents, preferably acetone;

(ii) adding aqueous hydrochloric acid solution;

(iii) heating the reaction mixture to reflux temperature and further stirring for 1-2 hours;

(iv) cooling the reaction mixture to ambient temperature;

(v) filtering the solid by conventional methods and further drying at 50-100^{O}C to a constant weight to afford the title crystalline solid.

10. The process according to claim 9 in step (i), wherein ketone is acetone.

11. A Novel crystalline Form of Ziprasidone.

12. The Novel crystalline Form of Ziprasidone according to claim 11 characterized by the X-ray powder diffraction pattern: (d values in A^{o}): 16.335, 12.209, 25.156, 27.019, 24.21, 5.255 and 18.511two-theta degrees.

13. The crystalline Form of Ziprasidone of claim 11 and 12 having X- ray powder diffraction pattern substantially as depicted in Figure (3).

14. The process for the preparation of novel crystalline form of Ziprasidone comprises:

a) Condensing 6-Chloro-5-(2-Chloroethyl) Oxindole with 3-(1-piperazinyl)-1,2-benzisothiozole in water using sodium carbonate;

b) purifiying in acetone to afford the crude Ziprasidone.

c) adding methane sulfonic acid in alcoholic media, preferably methanol media to crude Ziprasidone to afford the mesylate salt;

d) thus desaltifing the resulted salt with caustic lye in water media to afford the novel crystalline form.

15. The process according to claim 14 step (c), wherein alcoholic media is methanol.

16. Amorphous form of Ziprasidone hydrochloride, Novel crystalline Form of Ziprasidone hydrochloride monohydrate II and Novel crystalline Form of Ziprasidone, which are substantially as here in, described and exemplified.

Dated: 28th the day of November 2003

(Signed) S. Venkatraman

Sundaram Venkatraman
Vice-President-R&D
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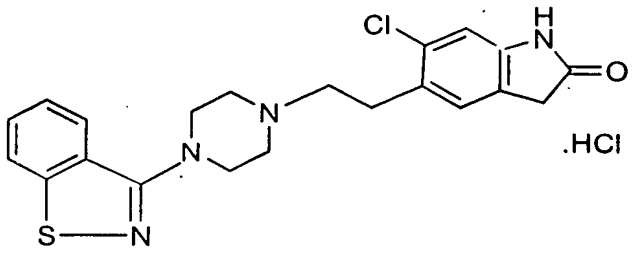
ABSTRACT

Title of the Invention: "Novel Polymorphic forms of Ziprasidone hydrochloride and Process for preparation thereof"

The present invention relates to novel polymorphic forms of Ziprasidone and its hydrochloride, which is chemically known as 5-(2-(4-(1,2-benzisothiozole-3yl)-piperazinyl) ethyl) - 6- chloro-1, 3-dihydro-2H-indole-2-one hydrochloride and shown as Formula (I), represented by the following structure.



Formula (I)

The present invention provides novel amorphous form of Ziprasidone hydrochloride, novel crystalline form of Ziprasidone and its hydrochloride, and process for preparation thereof.

The process for the preparation of novel amorphous form of the present invention comprises the addition of aqueous hydrochloric acid to the reaction mixture of Ziprasidone in acetic acid as a solvent at 40-50^{o}C, adding water and an alcoholic solvent then further heating to reflux temperature, distillating the solvents completely under reduced pressure to afford the desired amorphous form.

The process for the preparation of crystalline Form-II of the present invention comprises the addition of aqueous hydrochloric acid to the reaction mixture of Ziprasidone in ketone solvents and further heating to reflux temperature, filtering the desired crystalline compound at ambient temperature.

The novel crystalline form of Ziprasidone hydrochloride of present invention is designated as crystalline Form-II of Ziprasidone hydrochloride monohydrate.

The process for the preparation of novel crystalline form of Ziprasidone comprises the condensation of 6-Chloro-5-(2-Chloroethyl) Oxindole with 3-(1-piperazinyl)-1,2-benzisothiozole in water using sodium carbonate and it is purified in acetone to afford the crude Ziprasidone. The crude Ziprasidone is treated with methane sulfonic acid in methanol media to afford the mesylate salt, thus resulted salt is desaltified with caustic lye in water media to afford the novel crystalline form.

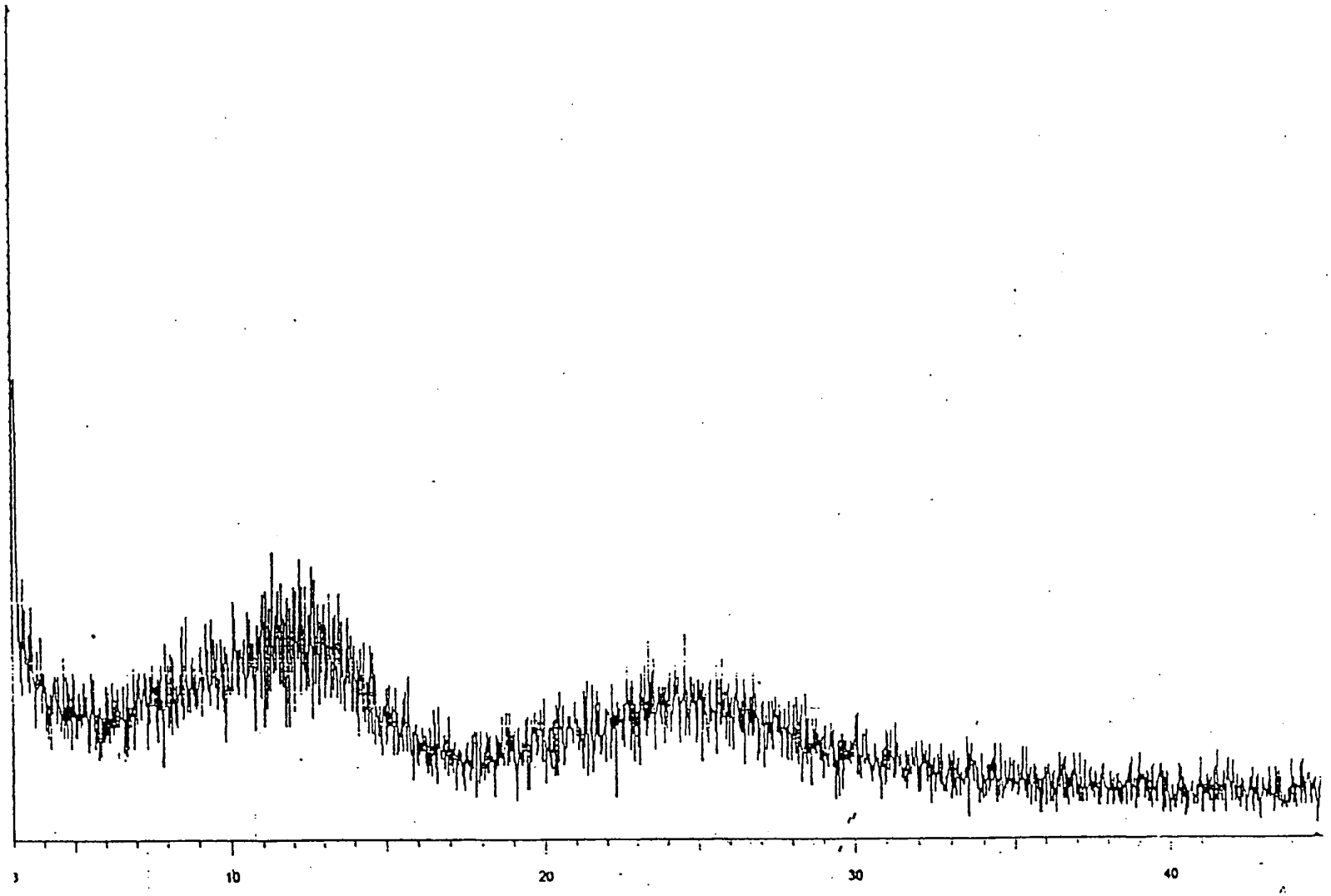


Fig.1

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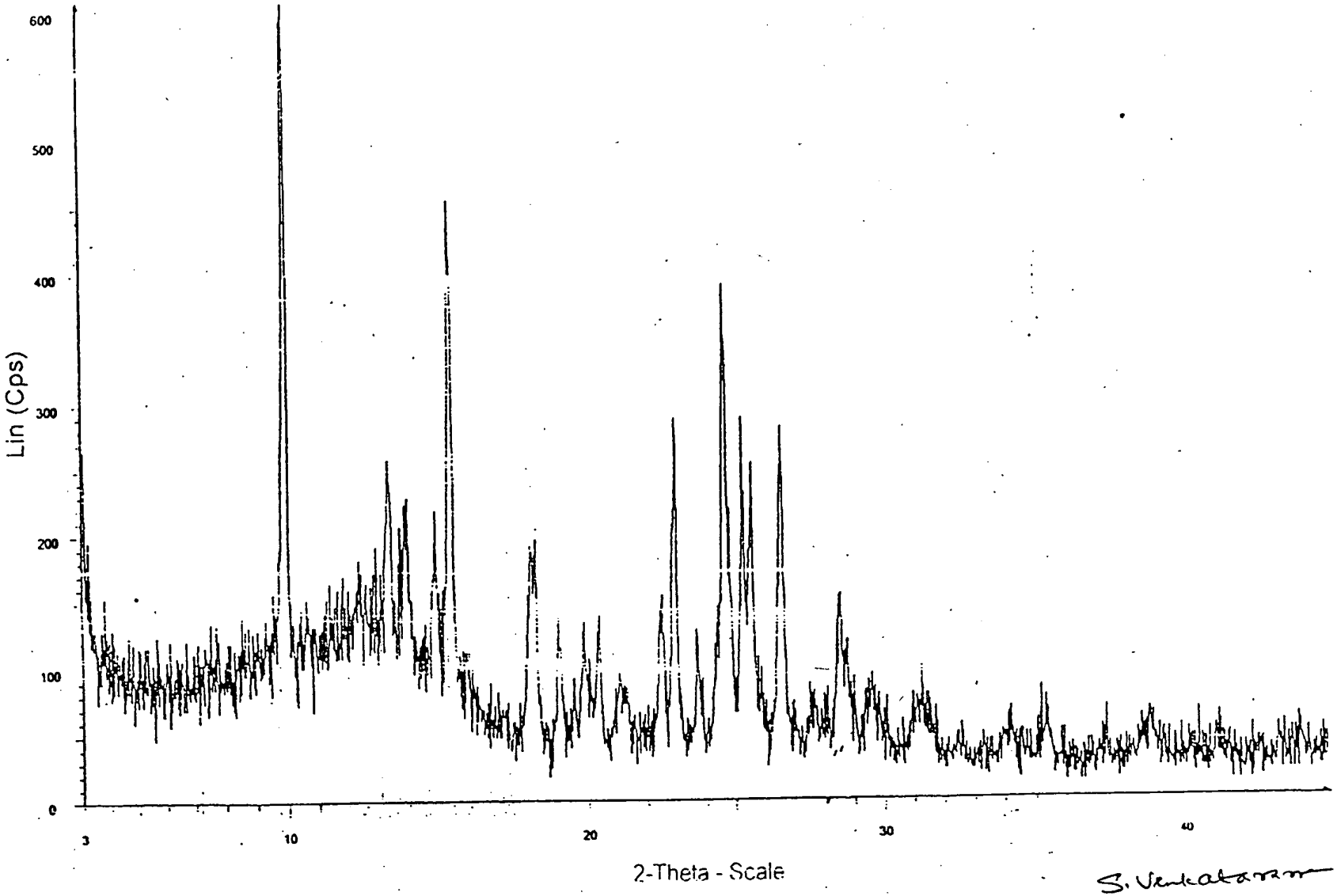

Fig. 2

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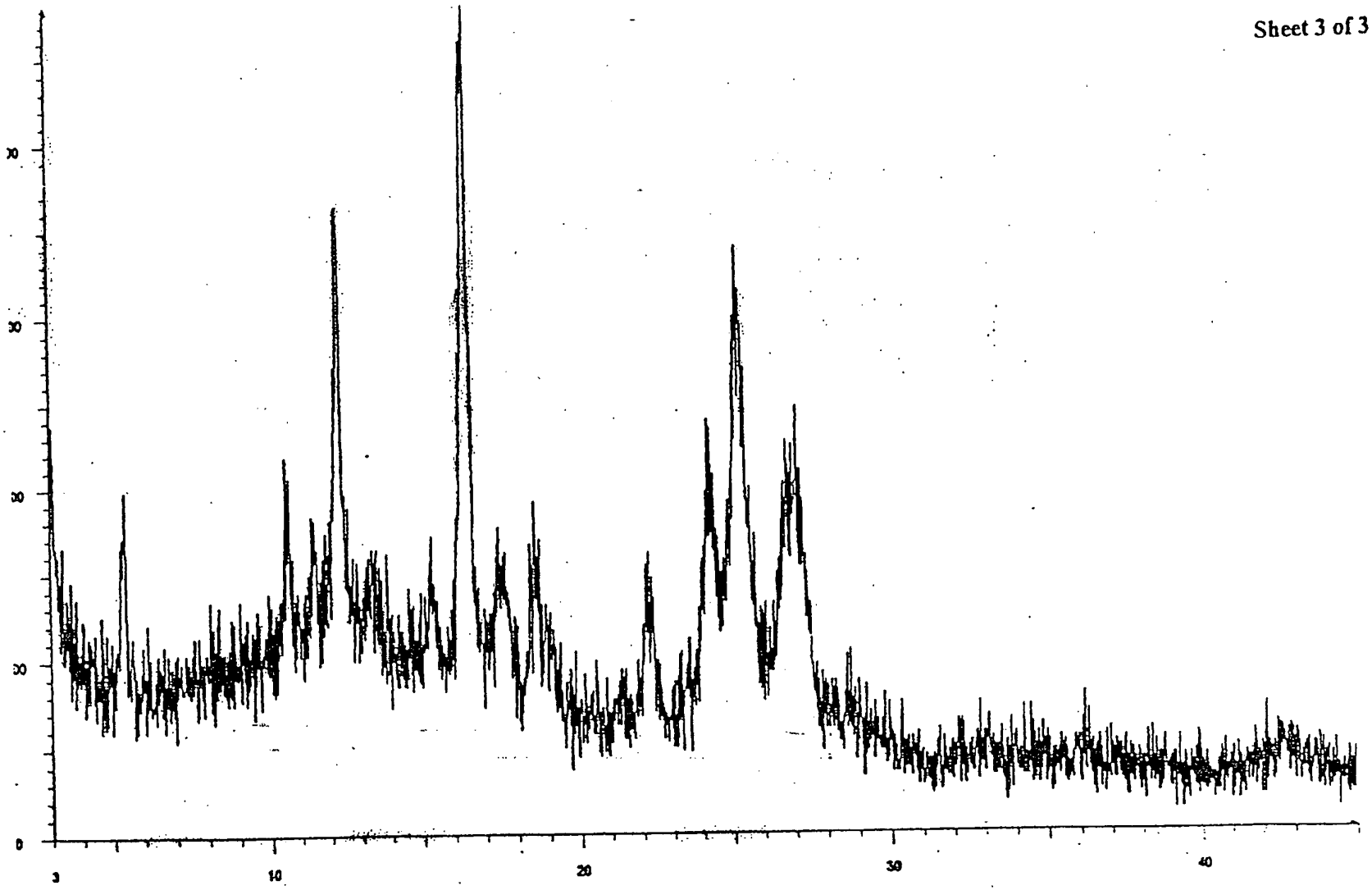

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Fig. 3